Influence of the duration of penicillin prescriptions on outcomes for acute sore throat in adults: results from the DESCARTE prospective cohort study

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*DESCARTE stands for Decision rule for the Symptoms and Complications of Acute Red Throat in Everyday practice

Abstract

Background. Guidelines recommend 10 day treatment courses for acute sore throat but shorter courses may be used in practice.

Aim. To determine whether antibiotic duration predicts adverse outcome of acute sore throat in adults in routine care.

Design and setting A secondary analysis of a prospective cohort study of 14610 adults presenting with acute sore throat in primary care.

Methods. A brief clinical proforma was used to collect symptom severity and examination findings at presentation. Outcomes were collected by notes review and in a sample a symptom diary.

Primary outcome: Re-consultation with new/non-resolving symptoms within 1 month. Secondary outcome 'global' poorer symptom control (longer than the median duration or higher than median severity).

Results. Antibiotics were prescribed for 60% (8572/14610) of participants. The most commonly prescribed antibiotic was phenoxymethylpenicillin (76%, 5656/7474) and prescription durations were largely for 5 (20%), 7 (57%), or 10 (22%) days.. Compared with 5 day courses those receiving longer courses were less likely to re-consult with new or non- resolving symptoms (5 days 15.3%, 7 days 13.9%, 10 days 12.2%, 7 day course adjusted risk ratio 0·92 (0·76, 1·11) and 10 days 0·86 (0·59, 1·23)) but these differences did not reach statistical significance.

Conclusions. In adults prescribed antibiotics for sore throat, we cannot rule out a small advantage in terms of reduced re-consultation for a 10 day course of penicillin but the effect is likely to be small.

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Introduction.

Acute sore throat is a common illness in everyday primary care practice and most patients are still prescribed antibiotics.[1-3] Current UK guidelines recommend a 'no' or 'delayed' prescribing approach[4] but when antibiotics are indicated then guidelines recommend ten days of penicillin in order to reduce the risk of relapse (PHE[5], ESCMID[6],SIGN[7], IDSA[8]).This recommendation for long antibiotic courses first appeared in the 1950s at a time when streptococcal complications were common and based on observing the eradication of streptococci in asymptomatic carriers,[9].[10-13]. However, this evidence may not be directly applicable to modern care in more economically developed countries for a number of reasons: streptococcal disease has changed over time; studies were largely in children;[10-13] used low doses of penicillin;[10] were restricted to those with proven streptococcal infection; [10,11] used stringent assessments of compliance;[12] and used bacteriological rather than clinical cure.[10,11] Only one study found a significant increase in recurrent symptoms after a shorter antibiotic course.[12] In a study in adults comparing placebo with three and seven days of antibiotic treatment, seven days gave superior symptom control and bacteriological eradication rates. Recurrent sore throats were most frequent in the 3 day group but there was no difference in re-attendance rates between the groups.[14] A Cochrane review of longer penicillin courses vs short courses of other antibiotic classes in children found superior symptomatic benefit with short courses with comparable other outcomes.[15] There are potential harms arising from greater exposure to courses of penicillin which is linked to subsequent carriage of resistant pneumococci[16] and carriage of resistant commensal organisms.[17] Not all guidelines recommend such prolonged treatment, the Dutch guidelines recommend seven day treatment and no longer recommends ten days for eradication of bacteria.[19] So if shorter courses lead to effective symptom relief without an increase in recurrence it should be possible to significantly reduce the volume of antibiotics prescribed.

Systematic reviews and randomised trials of antibiotics for acute sore throat have found only a modest effect on symptoms.[21] However, prescribing antibiotics may still be indicated in some instances.[21] It is important not to deny the benefit of antibiotics to patients at significant risk of severe illness or complications. We need evidence about appropriate duration of the antibiotic treatment for acute sore throat in adults in the modern era.

We therefore aimed to describe current antibiotic prescribing for sore throat in UK practice and to investigate whether duration of treatment or class of antibiotic was associated with adverse symptomatic outcome or increased re-consultation during the subsequent month using a large observational cohort which had been recruited to investigate potential prediction of septic complications of acute sore throat[22].

Methods.

Overall study design.

As previously reported[22,23], the study used a simple one page paper/web based case report form (CRF) documenting clinical features to facilitate assembly of a large prospective cohort of patients presenting with acute sore throat. The nested studies were two consecutive diagnostic cohorts (n=1107) to develop and validate a clinical score to predict bacterial infection[25] and a randomised trial (n=1781) which compared the use of the clinical score and the targeted use of a rapid antigen detection test with delayed antibiotic prescribing.[27] Trial participants were not included in the present analysis because their treatment had been allocated according to the trial protocol. Initial recruitment was among six local Networks (based in Southampton, Bristol, Birmingham Oxford, Cardiff, Exeter) but was extended nationally during the last 18 months of recruitment.

Patient inclusion criteria. Previously well subjects aged 16 years and over, presenting with acute (14 days or less) sore throat as the main symptom, with an abnormal examination of the pharynx (identical criteria to our previous studies).[28] Exclusion criteria were severe mental health problems (e.g. cognitive impairment and unable to consent or assess history) and known immune suppression.

Baseline clinical proforma. Age, gender, current smoking status, prior duration of illness and the presence and severity of baseline symptoms (sore throat, difficulty swallowing, fever during the illness, runny nose, cough, feeling unwell, diarrhoea, vomiting, abdominal pain, headache, muscles ache, sleep disturbance, earache) were documented on the CRF. Symptoms were recorded using 4 point Likert scales (none, a slight problem, a moderately bad problem, a severe problem), and the presence of signs (pus, nodes, cervical nodes, temperature, fetor, palatal oedema, difficulty speaking due to sore throat). The recruiting physician recorded antibiotic type and duration in the CRF.

Progression/non resolution of illness This was defined as re-consultation with non-resolving symptoms or development of a new respiratory diagnosis/symptom/sign within a month of the index presentation - similar to outcomes used previously in a trial of antibiotics for lower respiratory infection in adults[29] and in a cohort of children and ascertained using notes review.[30] Practice staff collected this outcome retrospectively and research staff who were not blinded to the treatment used and is available for the whole cohort.

Documentation of symptomatic outcome

A symptom diary was randomly allocated to a proportion of those recruited to the study to achieve the pre-specified target of 1800 diaries. The diary was similar to that used in other studies. [28,31] Patients completed the diary each night until symptoms resolved or up to 14 nights. Each symptom sore throat, difficulty swallowing, feeling unwell, fevers, sleep disturbance was scored (0=no problem to 6=as bad as it could be): Symptomatic outcomes were only available for those returning diaries.

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Sample size. Sample size calculations for the main study were based on the prediction of complications- a rare outcome. For the proposed analysis of diary data a sample of 1800 patients allowing for 20% loss to follow-up of diaries (900 of whom would not be expected to have antibiotics), would have power to detect variables with prevalences of 20% to 80% with an odds ratio of 2 for adverse symptomatic outcome among the no antibiotic group. Adverse symptomatic outcome was defined as severe symptoms or prolonged symptoms.

Outcomes

Primary outcome: Re-consultation with progression or non-resolution of illness within one month of the index consultation.

Secondary outcomes: Only determined in those with diary data, worse symptomatic outcomes (above median for either duration or severity of illness, duration of moderately bad symptoms, symptom severity on day 2-4, worsening of illness)

All outcomes reported in relation to prescribed antibiotic duration.

Analysis. All analyses were based on reported treatment at the index consultation. The subgroup analyses reported in this paper were specified in advance. Duration of symptoms was analysed using Cox regression, linear regression was used for symptom severity and generalised linear regression model with a log link for re-consultation and adverse symptomatic outcome. We have reported both the univariate statistics as well as the relationships after controlling for the severity of all baseline symptoms, antibiotic type (immediate or delayed) and clustering of patients by practice. To control for potential confounding by indication, we calculated a propensity score based on predictors of antibiotic prescribing. The propensity score was calculated based on variables which were significant predictors ($p<0.05$) of antibiotic prescribing strategy (5 days/7 days/10 days) in a multinomial logit model (mlogit in Stata) and was then included as an additional covariate in the prior models. This method was chosen in preference to propensity score matching since the outcome measure is categorical and therefore the analysis is more complex than for binary logistic models where propensity score matching might make sense[32]. The predicted probability from this model was then used as the propensity score in the analysis of the relationship between prescribing strategy and the study outcome measures. In order to explore whether those with higher probability of streptococcal infection experienced differential benefit from antibiotics we used the Centor score and the FeverPAIN score. The Centor score derived in hospital outpatients is used to predict the probability of Streptococcal infection, has been shown to be related to response to antibiotics and is widely used internationally.[33,34] The FeverPAIN score may also be used to predict the probability of streptococcal infection (A,C&G) in community samples and has been shown to be highly predictive of time to symptom resolution and symptom severity.[25] The FeverPAIN score comprises fever in the past 24 hours, purulence, rapid attendance (within three days), inflamed tonsils and no cough or cold symptoms. We tested for an interaction between Centor/FeverPAIN and symptom severity. We also used the Centor/FeverPAIN score to dicotomise the sample into those more or less likely to have a streptococcal infection, we used the cut point of 3 and above for Centor which is widely used to direct antibiotic prescribing and for FeverPAIN 0-2 vs 3 and over. For Centor the probability of a streptococcus swab positive result is 15% for those with a score of 2 and 32% for those with a score of 3 or above[33], for FeverPAIN risk of positive streptococcal swab is 26% for those with a score of 0 1 or 2 and for a score of

3 and above it is 60%.[25] Results are presented both for complete cases and for models with significant predictors of the propensity score imputed using a chained equations multiple imputation model. Outcome measures were not imputed as it was not possible to distinguish between individuals who were missing data because they did not complete a diary when asked and those who were not asked to complete one.

Analyses were carried out in Stata version 12.1.

Results.

14610 adult patients were recruited between 10th November 2006 and the 1st June 2009 from 616 general practices. 1629/2876 (57%) of those requested returned the symptom diary. There were no substantial differences in baseline characteristics between those returning the symptom diary and the main sample (Ref delayed paper). The inter-rater reliability for assessing return with non-resolution of symptoms was good (kappa 0.84).[24] Those receiving shorter courses of antibiotics were less likely to have a history of fever in the past 24 hours and less likely to have severely inflamed tonsils or pus on the tonsils (Table 1) and hence a lower Centor and FeverPAIN score. Those receiving antibiotics other than penicillin also had less severe symptoms (Appendix Table 1). Those given immediate antibiotics had more severe symptoms at baseline and were more likely to have a history of fever and severe inflammation or pus on tonsils (ref delayed paper).

Table 1

Immediate antibiotics were prescribed for 6088/14610 (42%) and delayed antibiotics for 2484/14610 (18 %). The most commonly prescribed antibiotic was phenoxymethylpenicillin (76% 5656/7474) and the majority of these prescriptions were for three durations; 5 (20%), 7 (57%), or 10 (22%) days. The proportions of antibiotic class and duration in those returning a diary were not different from the main sample (Appendix Table 2), From the diary data of those reporting taking the antibiotics (n=956); those prescribed a course of 10 days reported taking antibiotics for 9·33 days (s.d.1·73); those prescribed a course of 7 days reported taking antibiotics for 7·01 days (SD 2·14) and those prescribed a course of 5 days reported taking them for 5·75 days (SD 2·04).

Table 2

When adjusting for propensity to prescribe antibiotics, those prescribed longer courses of antibiotics re-consulted less often during the month following the index consultation compared to those prescribed a 5 day prescription. However, this difference was not statistically significant (7 days: RR 0·92 (95% CI 0·76, 1·11; p=0·377); 10 days: RR 0·86 (0·59, 1·23; p=0·408). Similar results were observed when adjusting for baseline severity and controlling for clustering of patients by practice (Table 2). Antibiotics other than penicillin were associated with a significantly greater risk of re-consultation (Table 2).

When controlling for propensity to prescribe or baseline severity and using five day prescription as comparator (Table 3), outcomes were similar in those prescribed seven days antibiotics. In those prescribed antibiotics for ten days,

adverse symptomatic outcomes were similar when controlling for baseline differences 1·13 (0·95, 1·35; p=0.·162) but were slightly worse when adjusting for propensity to prescribe 1·22 (1·02, 1·46; p=0·026) Those prescribed phenoxymethylpenicillin experienced similar symptomatic outcomes compared to those receiving antibiotics other than penicillin (Table 3).

Table 3

When tested independently neither the severity of symptoms on day 2-4 nor the duration of moderately bad symptoms was related to duration of prescription issued nor the class of antibiotic prescribed (Table 4 and Table 5 Figure 1).

Table 4

Table 5

Figure 1 Proportion experiencing symptoms rated moderately bad or worse according to duration of prescribed antibiotics

With the exception of the mean symptom severity score there was no evidence of an interaction between FeverPAIN score and outcomes related to the duration of antibiotic prescription. There was no evidence of any interaction between FeverPAIN score and outcomes related to antibiotic type. (Appendix Tables 3 and 4)
There was no evidence of any interaction between Centor score and outcomes related to the duration of antibiotic prescription nor on outcomes related to antibiotic type (Appendix tables 5 and 6)

Discussion.

Summary

This large observational cohort of patients enabled us to explore the effect of prescribing antibiotics in routine practice on re-consultation and symptom resolution. Although a seven day course is most often prescribed, five and ten day courses each accounted for approximately one fifth of prescriptions. Compared with a five day course those prescribed a ten day course appeared to have slightly worse global symptomatic outcome (longer than the median duration or higher than median severity) after adjustment for propensity to prescribe, the re-consultation rate was higher with shorter courses but this difference did not reach statistical significance. Current guidelines recommending penicillin treatment for ten days are not supported by these findings where the purpose is to provide symptom relief rather than bacterial eradication.
There is no evidence that phenoxymethylpenicillin is inferior to other antibiotic classes for symptom control, and given low rates of penicillin non-susceptibility of typical bacterial pathogens, it should be the first choice antibiotic. The implications for symptomatic benefit and re-consultation are similar for those predicted to be more or less likely to have a streptococcal throat infection using symptom scores.

Strengths and limitations

The study was designed using a simple template to minimise selection bias and thus to produce a large generaliseable prospective cohort. Recruitment of patients with acute illness is constrained by time issues and in common with other studies of acute infection[35-37] documentation of those not approached was poor (since time pressure to recruit also meant time pressure to document non recruitment). The large sample prospectively recruited in routine practice with the inclusion of diary data enabled the study of different antibiotic classes and duration of prescription both on re-consultation and on symptomatic outcomes, which is likely to reflect the real life experience of patients. As previously reported (ref delayed paper) there is evidence of a greater propensity to prescribe for those with more severe symptoms at baseline and a longer duration of antibiotics was also more likely in those with more severe symptoms. We have adjusted for propensity to prescribe and for baseline severity of symptoms in our analysis but cannot rule out residual confounding. Those who completed and returned the symptom diary may represent a more adherent population more generally so estimates of medication adherence may be inflated compared to the general population. The assessors of re-consultation were not blinded to the treatment allocation, which would have been available in the clinical record, since the primary aim of the cohort was to assess risk factors for septic complications we think it unlikely this would introduce any bias in recording of re-consultation. The reported duration of antibiotic consumption in those prescribed five days appears longer than that dispensed but this is an artefact as each day antibiotics were taken were included and hence the average reflects the final doses being on day six. Those prescribed antibiotics other than penicillin experience similar symptomatic outcomes but were at greater risk of re-consultation, this may reflect factors not controlled for in the analysis which determined the antibiotic choice. In recent years Fusobacterium necrophorum has emerged as a relevant pathogen in recurrent and severe sore throat, [38]although it may be isolated from 10% of community samples[39] and may be rarely associated with severe infection its precise contribution to acute uncomplicated sore throat illness is hard to ascertain. The analysis adjusted for propensity to prescribe and the negative interaction terms for Centor and FeverPAIN suggest that the adjustment took account of streptococcal infection (that there was no evidence of differential outcomes in those more likely to have streptococcal infection after adjustment) however these scores will not account for F. necrophorum and hence we can not

rule out residual confounding and this may account for the small difference in re-attendance (5 days 15.3% 10 days 12.2%). It is of note however that the use of broad spectrum antibiotics was not associated with improved outcomes. Whilst the results fail to show superiority of longer courses of penicillin for symptom relief or re-consultation this is not the same as equivalence and may reflect a lack of power.

Comparison with existing literature

The most commonly prescribed antibiotic was phenoxymethylpenicillin but there was variation in the duration of the prescription, with the majority receiving seven days (52%) – an observation which is at odds with the recommendations of current guidelines.[5] Although prescribing rates are similar, broad spectrum antibiotic prescribing is higher in the US (86% antibiotics other than penicillin or erythromycin.[20]) The prescription of five or seven day duration antibiotics did not appear to confer any significant increase in re-consultation in the month following the index consultation nor any worse symptomatic outcomes. A systematic review of studies in children found no difference in clinical outcomes after shorter courses of antibiotics but the comparison groups were ten days of penicillin compared with shorter courses of other antibiotic classes[15] and so is not directly comparable. There is a paucity of trial data in adults but one trial identified showed superiority of seven over three days treatment with penicillin.[14]

We examined the effect of antibiotics other than penicillin and did not find convincing evidence of differential symptomatic outcome. Non- penicillin antibiotics were associated with higher re-consultation rates. In a Cochrane review of antibiotic type in acute sore throat, no differences in symptom resolution were observed but clinical relapse was less likely following cephalosporin treatment.[40]

Implications.

When antibiotics are indicated current guidelines recommend a ten day course. We found a ten day course of antibiotics was not associated with greater benefit on either risk of re-consultation or symptom control compared to five or seven days antibiotic duration. In situations where bacterial eradication is not specifically needed and where symptomatic cure is the goal, if a decision to prescribe is made then a shorter course of penicillin may be sufficient and this finding should be confirmed with a randomised controlled trial. These finding should not be generalised to areas with a higher incidence of acute rheumatic fever.

Table 1 Baseline characteristics by duration of antibiotic prescription in the whole cohort

	5 days	7 days	10 days
Baseline clinical assessment			
Mean severity of sore throat/difficulty swallowing on a 4 point Likert scale (SD)	3·27 (0·65)	3·26 (0·67)	3·18 (0·63)
Mean severity of all baseline symptoms on a 4 point Likert scale (SD)	2·18 (0·40)	2·15 (0·40)	2·12 (0·41)
Mean FeverPain score*	1·72 (1·30)	1·94 (1·32)	2·36 (1·18)
Mean Centor score	1.85 (1.09)	2.06 (1.10)	2.33 (1.01)
Prior duration in days (SD)	4·61 (3·57)	4·68 (4·22)	4·11 (3·36)
Age in years (SD)	33·16 (14·05)	33·88 (14·21)	32·35 (13·75)
Female gender	984/1466 (67·1%)	2832/4187 (67·6%)	1102/1632 (67·5%)
Smoker	356/1464 (24.3%)	966/4168 (23·2%)	285/1621 (17·6%)
Fever in last 24 hours	962/1458 (66·0%)	2816/4171 (67·5%)	1152/1630 (70·7%)
Temperature ºC (SD)	36·86 (0·72)	36·93 (0·72)	36 ·99 (0·68)
Pus on tonsils	648/1460 (44·4%)	2131/4170 (51·1%)	1050/1627 (64·5%)
Severely inflamed tonsils	209/1371 (15·2%)	816/3945 (20·7%)	325/1546 (21·0%)
Number of prior medical problems	0·27 (0·52)	0·25 (0·52)	0·23 (0·49)
Return within 4 weeks with new or worsening symptoms	222/1449 (15·3%)	577/4135 (13·9%)	198/1620 (12·2%)
Return within 4 weeks with complications	13/1449 (0·9%)	55/4135 (1·3%)	22/1620 (1·3%)

- FeverPAIN score comprises fever in the past 24 hours, purulence, rapid (within three days) attendance, inflamed tonsils and no cough or cold symptoms
- Centor score comprises a history of fever, pus on tonsils, enlarged glands and absence of cough

Table 2 Re-consultation with new or worsening symptoms in the month following the index consultation according to duration of antibiotic prescribed and antibiotic class

	Reported new or worsening symptoms	Univariate risks ratio (95% CI; p-value)	Risk ratio controlling for baseline severity, and clustering (95% CI, p-value)	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in the imputed dataset
Duration of antibiotic prescription					
5 days (reference category)	222/1449 (15·3%)	1·00	1·00	1·00	1·00
7 days	577/4135 (13·9%)	0·91 (0·75, 1·05) p=0·201	0·93 (0·78, 1·08) p=0·321|	0·92 (0·76, 1·11) p=0·377	0·92 (0·76, 1·10) p=0·360
10 days	198/1620 (12·2%)	0·80 (0·67, 0·95) p=0·013	0·81 (0·55, 1·19) p=0·287	0·86 (0·59, 1·23) p=0·408	0·85 (0·59, 1·23) p=0·395
Antibiotic class					
Phenoxymethylpenicillin (reference category)	725/5,624 (12·9%)	1·00	1·00	1·00	1·00
Other antibiotics	302/1847 (16·3%)	1.27 (1.12, 1.44) p<0.001	1.28 (1.11, 1.47) p=0.001	1·27 (1·11, 1·49) p=0·002	1·26 (1·09, 1·45) p=0·001

All models controlled for immediate or delayed prescribing and clustering of patients by practice

Table 3 Adverse symptomatic outcome (greater than median symptom severity in days 2-4 or greater than median duration of symptoms) according to duration of antibiotic prescribed and antibiotic class

	Poor symptomatic outcome	Univariate risk ratio (95% CI; p-value)	Risk ratio controlling for baseline severity, Antibiotic type (immediate or delayed) and clustering (95% CI, p-value)*	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in imputed dataset
Duration of antibiotic prescription					
5 days (reference category)	105/185 (56·8%)	1·00	1·00	1·00	
7 days	312/535 (58·3%)	1·03 (0·89, 1·19) p=0·713	1·03 (0·89, 1·20) p=0·685	1·06 (0·91, 1·23) p=0·443	1·06 (0·91, 1·23) p=0·462)
10 days	108/168 (64·3%)	1·13 (0·96, 1·34) p=0·148	1·13 (0·95, 1·35) p=0·162	1·22 (1·02, 1·46) p=0·026	1·22 (1·02, 1·46) p=0·026
Antibiotic class					
Phenoxymethylpenicillin (reference category)	419/ 714 (58·7%)	1·00	1·00	1·00	1·00
Other antibiotics	125/206 (60·7%)	1·03 (0·91, 1·17) p=0·603	1·04 (0·91, 1·18) p=0·547	0·98 (0·84, 1·12) p=0·807	0·94 (0·68, 1·32) p=0·733

*for duration, the model also controls for whether the antibiotics prescribed were immediate or delayed

Table 4 Symptom severity on day 2-4 according to duration of antibiotic prescribed and antibiotic class

	Mean symptom severity (SD)	Difference	Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	Difference controlling for propensity score	Difference controlling for propensity score in the imputed dataset
Duration of antibiotic prescription					
5 days (reference category)	2·00 (1·22)				
7 days	1·99 (1·21)	-0·01 (-0·22, 0·19; p=0·896)	0·01 (-0·18, 0·19; p=0.935)	0·06 (-0·13, 0·25; p=0·520)	0·05 (-0·14, 0·24; p=0·587)
10 days	2·10 (1·20)	0·10 (-0·15, 0·35; p=0·426)	0·13 (-0·14, 0·41; p=0·330)	0·21 (-0·06, 0·48, p=0·119)	0·20 (-0·06, 0·48; p=0·130)
Antibiotic class					
Phenoxymethylpenicillin (reference category)	2·01 (1·22)				
Other antibiotics	2·02 (1·15)	0·01 (-0·17, 0·20; p=0·897)	0·02 (-0·17, 0·21; p=0·826)	0·00 (-0·20, 0·19; p=0·965)	-0·02 (-0·21, 0·16; p=0·796)

Table 5 Duration of moderately bad symptoms according to duration of antibiotic prescribed and antibiotic class

	Duration of moderately bad symptoms: median days (IQR)	**Univariate Risk ratio**	**Hazard ratio controlling for clustering, Antibiotic type (immediate or delayed) and baseline severity score (CI; p-value)**	**Hazard ratio controlling for propensity score**	**Hazard ratio controlling for propensity score in imputed dataset**
Duration of antibiotic prescription					
5 days (reference category)	3 (2,5)	1·00	1·00	1·00	1,00
7 days	3 (2,5)	1·06 (0·89, 1·27) p=0·527	1·05 (0·91, 1·23) p=0·488	1·05 (0·90, 1·23) p=0·513	1·07 (0·91, 1·25) p=0·418
10 days	3 (2,5)	0·99 (0·79, 1·24) p=0·957	0·99 (0·83, 1·20) p=0·963)	0·92 (0·74, 1·14) p=0·432	0·92 (0·73, 1·15) p=0·460
Antibiotic class					
Phenoxymethylpenicillin (reference category)	3 (2,5)	1·00	1·00	1·00	1·00
Other antibiotics	3 (2,5)	0·94 (0·80, 1·10) p=0·435	0·94 (0·82, 1·07) p=0·350	1·03 (0·88, 1·21) p=0·698	1·04 (0·89, 1·21) p=0·631

How this fits in:

- Antibiotics are not usually indicated for acute sore throat
- When streptococcal infection is probable or the risk of complications high, antibiotics are indicated and a ten day course is usually recommended
- We found evidence that a shorter duration of antibiotic prescription (five days) is associated with similar symptomatic outcomes and without increased risk of re-consultation when compared with longer courses of antibiotic
- These findings should be confirmed with a randomised controlled trial since exposure to antibiotics could be potentially reduced if confirmed.

Contributorship

DESCARTE Investigators:

Michael Moore (GP and Professor in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study, and led the drafting of the paper
Chris Butler (Professor of Primary Care, Cardiff and Oxford Universities) developed the protocol for funding, supervised the running of the study in the Cardiff Network and contributed to the drafting of the paper
Paula Barratt and Sue Broomfield (senior study managers) developed the protocol, provided day to day overall management of the study, coordinated recruitment in the lead study centre and coordination of other centres, commented on drafts of the paper.
John Campbell (GP and Professor of Primary Care, University of Exeter) developed the protocol for funding, lead the running of the study in the Exeter Network and contributed to the drafting of the paper
Brendan Delaney (GP and Chair in Medical Informatics and Decision Making, Imperial College, London) developed the protocol for funding, coordinated the development and management of the web resource, and contributed to drafting of the paper..
Hazel Everitt (Associate Professor, University of Southampton) developed the protocol, with SB led the reliability study, supervised data collection for the reliability study, contributed to analysis and contributed to drafting the paper
Alastair Hay (GP and Professor of Primary Care, University of Bristol) developed the protocol for funding, led the Bristol study centre and contributed to the analysis and the drafting of the paper
F.D.R. Hobbs FMed Sci Nuffield Department of Primary Care Health Sciences, University of Oxford, and supported by NIHR SPCR, Oxford CLAHRC, Oxford BRC and Harris Manchester College developed the protocol for funding, led the Birmingham study centre and contributed to the drafting of the paper
Paul Little (GP and Professor of Primary Care Research, University of Southampton) had the original idea for the protocol, led protocol development and the funding application, supervised the running of the lead study centre and coordination of centres, contributed to the analysis, and contributed to the drafting of the paper
David Mant Emeritus Professor of General Practice, University of Oxford) developed the protocol for funding, supervised the running of clinical studies in the Oxford centre and contributed to the analysis and the drafting of the paper
Mark Mullee (study Statistician, Director Research Design Service, University of Southampton) developed the protocol for funding, contributed to study management, supervised data management, shared the quantitative analysis with BS and PL and contributed to the drafting of the paper
Beth Stuart (study Statistician, University of Southampton) developed the protocol, and led the quantitative analysis with MM and PL, and with MM drafted the initial versions of the paper.
Ian Williamson (GP and Associate Professor in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study and drafting of the paper
Kerenza Hood (Director of South East Wales Trials Unit, Cardiff University). Contributed to protocol development, supervised the running of the study in the Cardiff Network and contributed to the drafting of the paper.

Other Contributors:

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Ethical approval was given by the South West Multicentre Research Ethics Committee (number 06/MRE06/17).

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MM is the guarantor of the paper and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Data sharing: no additional data available.

Patient involvement
No patients were involved in the design of this study

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Appendix Table 1

Baseline characteristics by Antibiotic type

	Phenoxymethylpenicillin N=5696	**Other N=1857**
Clinical assessment		
Mean severity of sore throat/difficulty swallowing on a 4 point Likert scale (SD)	3·28 (0·64)	3·13 (0·70)
Mean severity of all baseline symptoms* on a 4 point Likert scale (SD)	2·15 (0·40)	2·14 (0·40)
Mean FeverPain score	2·12 (1·28)	1·57 (1·28)
Mean Centor Score	2.45 (0.97)	1.97 (1.05)
Prior duration in days (SD)	4·36 (3·60)	5·14 (4·94)
Age in years (SD)	32·25 (13·60)	37·01 (14·95)
Female	3,835/5696 (67·3%)	1,265/1,857 (68·1%)
Smoker	1,296/5663 (22·9%)	384/1850 (20·8%)
Fever in last 24 hours	3897/5672 (68·7%)	1,213/1841 (65·9%)
Temperature ºC (SD)	36·95 (0·71)	36·87 (0·73)
Pus on tonsils	3,225/5,668 (56·9%)	718/1841 (39·0%)
Severely inflamed tonsils	1,153/ 5,338 (21·6%)	234/1736 (13·5%)
Number of prior medical problems	0·23 (0·49)	0·31 (0·59)
Return within 4 weeks with new or worsening symptoms	725/ 5,624 (12·9%)	302/1,847 (16·3%)
Return within 4 weeks with complications	65/5,624 (1·2%)	28/1847 (1·5%)

Appendix Table 2 Type and duration of antibiotics issued comparison of those completing symptom diary with full cohort.

	Total cohort N=7474		**Patients who completed diaries N=922** [(i)]	
	Given antibiotics	**Delayed antibiotics**	**Given antibiotics**	**Delayed antibiotics**
Antibiotic type				
Phenoxymethylpenicillin	4354/5793 (75·2%)	1302/1681 (77·4%)	552 /725 (76·1%)	163/197 (82·7%)
Amoxicillin	601/5793 (10·4%)	165/1681 (9·8%)	78/725 (10·8%)	17/197 (8·6%)
Erythromycin	542/5793 (9·4%)	171/1681 (10·2%)	56/725 (7·7%)	11/197 (5·6%)
Other [(ii)]	296/5793 (5·1%)	43/1681 (2·6%)	39/725 (5·4%)	6/197 (3·0%)
Duration of course				
5 days	1,125/5,651 (19·9%)	327/1,631 (20·0%)	147/709 (20·7%)	36/191 (18·8%)
7 days	3222/5,651 (57·0%)	919/1,631 (56·3%)	427/709 (60·2%)	109/191 (57·1%)
10 days	1,249/5,651 (22·1%)	371/1,631 (22·7%)	127/709 (17·9%)	42/191 (22·0%)
Other duration	56/5651 (1·0%)	14/1631 (0·9%)	8/709 (1·1%)	4/191 (2·1%)
Took antibiotics [(iii)]			670/692 (96·8%)	115/191 (60·2%)
Mean number of days for which antibiotics were taken			7·07 (2.22)	7·12 (2.92)

(i) 922/1512 completed diaries and also prescribed antibiotics

(ii) Included cephalexin (191) co-amoxiclav (40) clarithromycin (38) and doxycycline (22)

(iii) There were an additional 105 people out of 554 (18·8%) who were not prescribed antibiotics who reported taking them.

Appendix Table 3

Effect of duration of antibiotic prescribing among those more likely to have streptococcal infection (FeverPAIN 3 or above) on poor symptomatic outcome, re-consultation, duration of symptoms and symptom severity.

		Interaction term	Univariate risk ratio (95% CI; p-value)	Risk ratio controlling for baseline severity and clustering (95% CI, p-value)*	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in imputed dataset
	Poor symptomatic outcome					
5 days	26/48 (54·2%)		1·00	1·00	1·00	1·00
7 days	86/282 (47·5%)	0.92 (0.82, 1.04; p=0.179)	0·88 (0·65, 1·19; p=0·395)	0·88 (0·65, 1·19; p=0·413)	0·93 (0·68, 1·27; p=0·652)	0·93 (0·68, 1·27; p=0·637)
10 days	48/72 (66·7%)	1.02 (0.91, 1.15; p=0.680)	1·23 (0·91, 1·67; p=0·185)	1·24 (0·94, 1·65; p=0·127)	1·29 (0·96, 1·74; p=0·088)	1·29 (0·96, 1·74; p=0·089)
	Re-consultation					
5 days	56/353 (15·9%)		1·00	1·00	1·00	1·00
7 days	177/1295 (13·7%)	0.98 (0.88, 1.09; p=0.657)	0·86 (0·65, 1·14; p=0·291)	0·85 (0·64, 1·164 p=0·273)	0·84 (0·63, 1·12; p=0·228)	0·85 (0·64, 1·12; p=0·243)
10 days	97/712 (13·6%)	1.03 (0.92, 1.16; p=0.609)	0·86 (0·63, 1·16; p=0·325)	0·89 (0·57, 1·38; p=0·609)	0·85 (0·56, 1·28; p=0·430)	0·85 (0·56, 1·28; p=0·434)
	Duration of symptoms					
5 days	3 (2,5)		1·00	1·00	1·00	1·00
7 days	3 (2,4)	1·06 (0·94, 1·19; p=0·378)	1·16 (0·82, 1·63; p=0·412)	1·14 (0·84, 1·56; p=0·403)	1·20 (0·87, 1·65; p=0·270)	1·20 (0·87, 1·66; p=0·262)
10 days	3 (2,5)	0.93 (0.81, 1.07; p=0.326)	0·84 (0·56, 1·25; p=0·385)	0·85 (0·61, 1·19; p=0·345)	0·90 (0·63, 1·27; p=0·539)	0·89 (0·63, 1·27; p=0·527)
	Mean symptom severity score		**Difference**	**Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)**	**Difference controlling for propensity score**	**Difference controlling for propensity score in the imputed dataset**
5 days	1·83 (1·18)					
7 days	1·85 (1.22)	0.01 (-0.12, 0.13; p=0.959)	0·02 (-0·37, 0·42; p=0·910)	0·04 (-0·29, 0·37; p=0·807)	0·09 (-0·26, 0·43; p=0·626)	0·08 (-0·27, 0·42; p=0·664)
10 days	2·31 (1·32)	0.18 (0.03, 0.33; p=0.018)	0·48 (0·03, 0·94; p=0·038)	0·48 (0·08, 0·88; p=0·018)	0·51 (0·10, 0·92; p=0·015)	0·51 (0·11, 0·92; p=0·013)

Appendix Table 4

Effect of antibiotic type among those more likely to have streptococcal infection (FeverPAIN 3 or above) on poor symptomatic outcomes, re-consultation, duration of symptoms and symptom severity (penicillin vs other)

		Interaction term (95% CI; p-value)	**Univariate risk ratio (95% CI; p-value)**	**Risk ratio controlling for baseline severity and clustering (95% CI, p-value)***	**Risk ratio controlling for propensity score**	**Risk ratio controlling for propensity score in imputed dataset**
	Poor symptomatic outcome					
Phenoxymethylpenicillin	138/260 (53·1%)		1·00	1·00	1·00	1·00
Other antibiotics	32/55 (58·2%)	1.04 (0.94, 1.13; p=0.463)	1·10 (0·85, 1·41; p=0·474)	1·10 (0·86, 1·39; p=0·450)	1·00 (0·88, 1·13; p=0·966)	1·08 (0·86, 1·35; p=0·503)
	Re-consultation					
Phenoxymethylpenicillin	267/2026 (13·2%)		1·00	1·00	1·00	1·00
Other antibiotics	67/396 (16·9%)	0·99 (0·74, 1·32; p=0·944)	1·28 (1·00, 1·64; p=0·046)	1·28 (0·99, 1·66; p0·064)	1·30 (1·00, 1·69; p=0·046)	1·28 (1·00, 1·64; p=0·049)
	Duration of symptoms					
Phenoxymethylpenicillin	3 (2,4)		1·00	1·00	1·00	1·00
Other antibiotics	3 (2,5)	1·05 (0·79 1·39; p=0.756)	1·00 (0·74, 1·36; p=0·983)	1·00 (0·79, 1·28; p=0·981)	1·05 (0·84, 1·32; p=0·670)	1·08 (0·86, 1·35; p=0·516)
	Mean symptom severity score		**Difference**	**Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)**	**Difference controlling for propensity score**	**Difference controlling for propensity score in the imputed dataset**
Phenoxymethylpenicillin	1.97 (1·25)					
Other antibiotics	1.93 (1·18)	-0·07 (-0·43, 0·29; p=0·699)	-0·04 (-0·40, 0·32; p=0·838)	-0·03 (-0·36, 0·31; p=0·882)	-0·10 (-0·45, 0·26; p=0·589)	-0·08 (-0·42, 0·26; p=0·651)

Appendix Table 5

Effect of duration of antibiotic prescribing among those more likely to have streptococcal infection (Centor 3 or above) on poor symptomatic outcome, re-consultation, duration of symptoms and symptom severity.

		Interaction term	**Univariate risk ratio (95% CI; p-value)**	**Risk ratio controlling for baseline severity and clustering (95% CI, p-value)***	**Risk ratio controlling for propensity score**	**Risk ratio controlling for propensity score in imputed dataset**
	Poor symptomatic outcome					
5 days	38/75 (50.7%)		1.00	1.00	1.00	1.00
7 days	122/242 (50.4%)	0.91 (0.68, 1.22; p=0.530)	0.99 (0.77, 1.29; p=0.969)	0.99 (0.78, 1.25; p=0.916)	1.01 (0.79, 1.29; p=0.933)	1.01 (0.79, 1.29; p=0.952)
10 days	58/88 (65.9%)	1.23 (0.89, 1.70; p=0.205)	1.30 (0.99, 1.70; p=0.055)	1.31 (1.02, 1.66; p=0.031)	1.36 (1.06, 1.73; p=0.014)	1.36 (1.06, 1.73; p=0.014)
	Re-consultation					
5 days	83/535 (15.5%)		1.00	1.00	1.00	1.00
7 days	260/1834 (14.2%)	1.03 (0.73, 1.45; p=0.877)	0.91 (0.73, 1.15; p=0.437)	0.92 (0.71, 1.21; p=0.564)	0.88 (0.66, 1.16; p=0.370)	0.88 (0.67, 1.16; p=0.375)
10 days	127/945 (13.4%)	1.25 (0.83, 1.88; p=0.264)	0.87 (0.67, 1.12; p=0.271)	0.90 (0.60, 1.34; p=0.599)	0.89 (0.60, 1.32; p=0.559)	0.89 (0.60, 1.31; p=0.557)
	Duration of symptoms					
5 days	3 (2,5)		1.00	1.00	1.00	1.00
7 days	3 (2,4)	1.15 (0.81, 1.61; p=0.440)	1.12 (0.85, 1.49; p=0.421)	1.13 (0.87, 1.45; p=0.354)	1.16 (0.90, 1.51; p=0.253)	1.17 (0.90, 1.51; p=0.245)
10 days	3 (2,5)	0.83 (0.57, 1.22; p=0.346)	0.89 (0.64, 1.24; p=0.482)	0.90 (0.67 1.19; p=0.449)	0.89 (0.65, 1.21; p=0.452)	0.89 (0.65, 1.20; p=0.441)
	Mean symptom severity score		**Difference**	**Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)**	**Difference controlling for propensity score**	**Difference controlling for propensity score in the imputed dataset**
5 days	1.90 (1.25)					
7 days	1.92 (1.29)	0.02 (-0.38, 0.43; p=0.908)	0.02 (-0.30, 0.35; p=0.896)	0.02 (-0.27, 0.31; p=0.906)	0.03 (-0.27, 0.34; p=0.823).	0.03 (-0.27, 0.33; p=0.857)
10 days	2.25 (1,22)	0.42 (-0.05, 0.89; p=0.083)	0.35 (-0.04, 0.74; p=0.078)	0.36 (=0.01, 0.73; p=0.053)	0.38 (0.003, 0.75; p=0.048)	0.38 (0.01, 0.75; p=0.046)

Appendix Table 6

Effect of antibiotic type among those more likely to have streptococcal infection (Centor 3 or above) on poor symptomatic outcomes, re-consultation, duration of symptoms and symptom severity (penicillin vs other)

		Interaction term (95% CI; p-value)	Univariate risk ratio (95% CI; p-value)	Risk ratio controlling for baseline severity and clustering (95% CI, p-value)*	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in imputed dataset
	Poor symptomatic outcome					
Phenoxymethylpenicillin	188/348 (54.0%)		1.00	1.00	1.00	1.00
Other antibiotics	39/70 (55.7%)	1.00 (0.77, 1.29; p=0.995)	1.03 (0.82, 1.30; p=0.793)	1.04 (0.85, 1.29; p=0.690)	1.01 (0.82, 1.23; p=0.955)	1.02 (0.83, 1.24; p=0.873)
	Re-consultation					
Phenoxymethylpenicillin	382/2835 (13.5%)		1.00	1.00	1.00	1.00
Other antibiotics	99/573 (17.3%)	0.97 (0.74, 1.28; p=0.832)	1.28 (1.05, 1.57; p=0.016)	1.28 (1.02, 1.61; p=0.036)	1.33 (1.05, 1.68; p=0.017)	1.29 (1.03, 1.62; p=0.026)
	Duration of symptoms					
Phenoxymethylpenicillin	3 (2,4)		1.00	1.00	1.00	1.00
Other antibiotics	3 (2,5)	1.03 (0.77, 1.37; p=0.843)	0.99 (0.75, 1.29; p=0.916)	1.00 (0.80, 1.25; p=0.980)	1.02 (0.81, 1.29; p=0.870)	1.03 (0.82, 1.30; p=0.783)
	Mean symptom severity score		Difference	Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	Difference controlling for propensity score	Difference controlling for propensity score in the imputed dataset
Phenoxymethylpenicillin	1.00 (1.26)					
Other antibiotics	1.96 (1.26)	-0.11 (-0.46, 0.24; p=0.538)	-0.03 (-0.36, 0.29; p=0.837)	-0.01 (-0.31, 0.29; p=0.934)	-0.06 (-0.37, 0.24; p=0.678)	-0.07 (-0.38, 0.24; p=0.655)